Pathophysiology of Systolic and Diastolic Heart Failure

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KEYWORDS

• Chronic heart failure • Systolic heart failure • Diastolic heart failure

KEY POINTS

- Systolic and diastolic heart failure are the 2 most common clinical subsets of chronic heart failure.
- Left ventricular "Starling" function is depressed in patients with systolic heart failure.
- In systolic heart failure, left ventricular mass is increased, which can be measured by transthoracic echocardiography. Cardiac magnetic resonance imaging is a more precise technique to measure left ventricular mass.
- Neurohormonal activation is a major pathophysiologic mechanism for ventricular remodeling and progression of heart failure in systolic heart failure.

HISTORICAL PERSPECTIVES

The differences between systolic and diastolic heart failure have been recognized for several decades. In 1937, Dr Fishberg described that diastolic heart failure results from inadequate ventricular filling, and he termed this type of heart failure as hypodiastolic failure. He also recognized that systolic heart failure results from inadequate emptying of the heart and he called it hyposystolic failure.[1]

Definitions

The most commonly used definition of systolic heart failure is that "it is a pathophysiologic state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues."[2] However, such a definition , although precise, is difficult to use in clinical practice. The definition of systolic heart failure that is used clinically is that it is "a syndrome which results from reduced left ventricular ejection fraction."[3] Systolic heart failure is also termed "heart failure with reduced ejection fraction" (HFREF). The pathophysiologic definition of diastolic heart failure is that "it is a condition resulting from an increased resistance to filling of one or both ventricles leading to symptoms of

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Med Clin N Am 96 (2012) 891–899
http://dx.doi.org/10.1016/j.mcna.2012.07.001 **medical.theclinics.com**
0025-7125/12/$ – see front matter Published by Elsevier Inc.

congestion due to an inappropriate shift of the diastolic-pressure volume relation (that is during the terminal phase of the cardiac cycle."[4]

The clinical definition of diastolic heart failure is that "it is a clinical syndrome characterized by the symptoms and signs of heart failure, a preserved left ventricular ejection fraction and abnormal diastolic function."[5] Diastolic heart failure is also termed "heart failure with preserved ejection fraction" (HFPEF). In this review, the terms systolic and diastolic heart failures are used instead of HFREF and HFPEF.

Pathophysiology

In systolic heart failure, the left ventricle is dilated and there is increase in both left ventricular end-diastolic and end-systolic volumes; but, as there is a greater increase in end-systolic than in end-diastolic volume, left ventricular ejection fraction is reduced. Ejection fraction is the ratio of left ventricular total stroke volume and its end-diastolic volume. Thus, when there is a disproportionate increase in end diastolic volume, ejection fraction may decline and the stroke volume may remain normal (**Fig. 1**A). Left ventricular stroke volume is the difference between end-diastolic and end-systolic volume. In some patients, when there is a disproportionate decrease in stroke volume, ejection fraction may decline despite normal left ventricular end-diastolic volume (see **Fig. 1**B).

There are substantial changes in the shape of the left ventricle. Normally, the left ventricle is ellipsoidal. In systolic heart failure, it becomes spherical. Changes to globular shape cause misalignment of the papillary muscles, chordate, and mitral valve leaflets, which is associated with mitral regurgitation. Mitral regurgitation causes further increase in left ventricular volumes and progressive remodeling.

In systolic heart failure, the left ventricular wall thickness remains unchanged or may decrease. The normal or decreased left ventricular wall thickness along with an increase in ventricular volumes is associated with increased wall stress (**Fig. 2**). There is an inverse relationship between wall stress and ejection fraction. The higher the wall stress, the lower is the ejection fraction. Thus, in patients with systolic heart failure, an increase in wall stress contributes to decreased ejection fraction. The major mechanism of reduced ejection fraction, however, is decreased contractility. The morphologic and functional changes in systolic heart failure are summarized in **Table 1**.

Left ventricular "Starling" function is depressed in patients with systolic heart failure. Ventricular "Starling" function is the relationship between its stroke volume

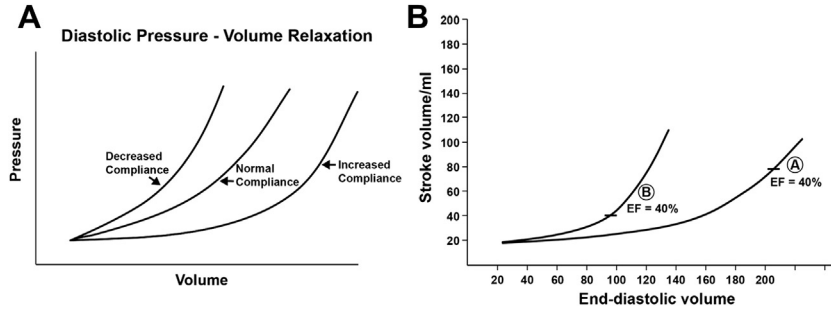

Fig. 1. Schematic illustrations of pressure (*vertical axis*) and volume (*horizontal axis*). When there is a disproportionate increase in end-diastolic volume, ejection fraction can be reduced with normal stroke volume (*A*). Ejection fraction may decrease to the same extent when there is a disproportionate decrease in stroke volume with normal end-diastolic volume (*B*).

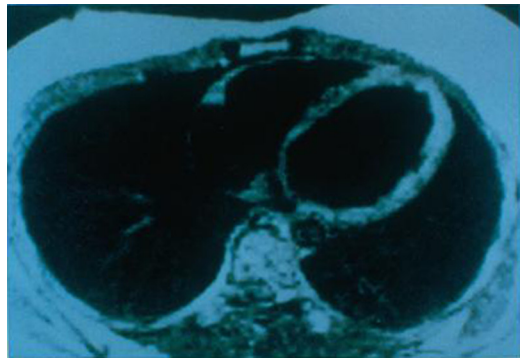

Fig. 2. Cardiac magnetic resonance image of a patient with systolic heart failure illustrating normal wall thickness and globular shape of the left ventricle.

and end-diastolic volume. In clinical practice, pulmonary capillary wedge pressure is used to represent left ventricular end-diastolic volume. In systolic heart failure, increased pulmonary capillary wedge pressure with reduced or normal stroke volume indicates depressed left ventricular "Starling" function (**Fig. 3**).

In systolic heart failure, left ventricular mass is increased, which can be measured by transthoracic echocardiography. Cardiac magnetic resonance imaging, however, is a more precise technique to measure left ventricular mass (see **Fig. 2**; see **Table 1**). Increased left ventricular mass is a result of left ventricular hypertrophy. Left ventricular mass cannot be detected by electrocardiography. The left ventricular cavity size is increased, which can also be detected by both echocardiography and cardiac magnetic resonance imaging. In systolic heart failure, left ventricular cavity size is markedly increased and the cavity/mass ratio is increased.

In patients with systolic heart failure, progressive left ventricular dilatation may occur, particularly in patients treated inadequately with pharmacotherapy of proven benefit. The angiotensin inhibitors, beta blockers, and aldosterone antagonists can attenuate progressive left ventricular dilatation and remodeling. Progressive ventricular dilatation is associated with worsening heart failure and poor prognosis.

In systolic heart failure, there are also substantial changes in the architecture of the extracellular matrix. The collagen fibrils are disrupted and disorganized. The collagen fibrils are thinner than normal.[6] Myocardial collagen volume and fibrosis increase in systolic heart failure. Circulating levels of procollagen are increased, which suggests abnormal collagen metabolism.[7]

Table 1
LV Mass volumes and EF in heart failure

	Normals	DCM
LV mass	79.5 ± 7.6	152.5 ± 31.1
LVEDV	62.3 ± 7.3	116.8 ± 28.4
LVESV	21.7 ± 3.9	71.6 ± 23.9
LVEF	65.1 ± 3.6	35.1 ± 2.4
Wall stress	43.0 ± 10.7	91.2 ± 20.2

Abbreviations: DCM, dilated cardiomyopathy; EDV, end-diastolic volume; ESV, end-systolic volume; LV, left ventricular; LVEF, left ventricular ejection fraction.

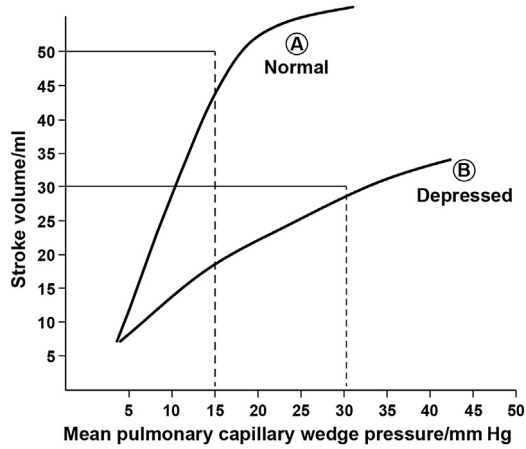

Fig. 3. Schematic illustration of left ventricular "Starling" function relating stroke volume (*vertical axis*) and pulmonary capillary wedge pressure (*horizontal axis*). In systolic heart failure, the ventricular function curve shifts downward and to the right. In diastolic heart failure, there is no shift of the ventricular function curve.

Neurohormonal Changes

Neurohormonal activation is a major pathophysiologic mechanism for ventricular remodeling and progression of heart failure in systolic heart failure.[8,9] There are increased levels of circulating catecholamines, such as norepinephrine and dopamine. There is also evidence for increased central nervous system–mediated activation of the sympathetic nervous system. The muscle sympathetic nerve activity is substantially increased in patients with systolic heart failure. The renin-angiotensin-aldosterone system is activated, as is evident from increased levels of plasma renin, angiotensin, and aldosterone. Angiotensin produces its deleterious effects by activation of angiotensin receptor subtype 1 receptors. There is vasoconstriction, and smooth muscle and myocyte hypertrophy. It also induces proinflammatory, mitogenic, and prothrombotic effects. Levels of vasopressins, endothelins, and cytokines, such as tumor necrosis factor-alpha, are also elevated. These neurohormones also induce vasoconstriction, and increase systemic vascular resistance, which is associated with deterioration in left ventricular systolic function. These neurohormones also exert proinflammatory, mitogenic, and prothrombotic effects. Aldosterone promotes collagen synthesis and fibrosis.

There is concurrent activation of vasodilatory, natriuretic, antimitogenic, and antithrombotic neurohormones. The levels of natriuretic peptides, such as B-type natriuretic peptide (BNP), nitric oxide, endothelium-derived relaxing factor, and prostacyclins are increased. It has been postulated that if the balance between these 2 systems is maintained, ventricular remodeling can be attenuated; however, progressive ventricular remodeling continues if there is an excessive activation of adrenergic and renin-angiotensin-aldosterone systems.

Hemodynamic Changes

The hemodynamic changes in systolic heart failure are characterized by an increase in pulmonary venous pressure secondary to increased left ventricular diastolic volumes. There is a passive increase in pulmonary artery pressure, which increases resistance to right ventricular emptying. As a result, right ventricular function deteriorates, which is clinically manifested by elevated jugular venous pressure (**Fig. 4**) and dependent

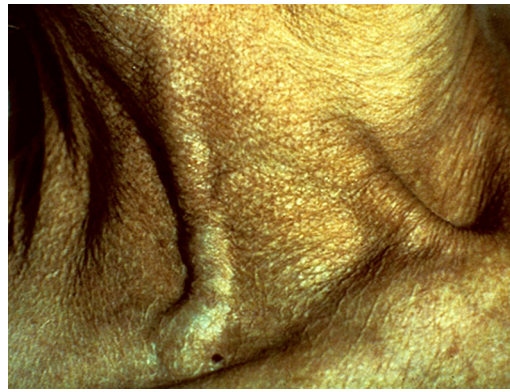

Fig. 4. Jugular venous distension in patients with heart failure is illustrated. Both external and internal jugular veins are distended owing to increased systemic venous pressure.

edema. With chronic elevation of pulmonary venous pressure, there is also an increase in pulmonary vascular resistance, which further increases right ventricular afterload. There may be a decrease in both right and left ventricular stroke volume, which is associated with signs and symptoms of low cardiac output. Left ventricular stroke volume decreases not only because of deceased contractility and increased afterload, but also because of decreased filling resulting from decreased right ventricular stroke volume, which contributes to left ventricular preload.

Mechanical dyssynchrony contributes to deranged hemodynamics in systolic heart failure. Mechanical dyssynchrony, in presence or absence of electrical dyssynchrony, is observed in approximately 30% to 40% of patients with systolic heart failure. When mechanical dyssynchrony is present, contraction and relaxation of the lateral wall occurs earlier than that of the interventricular septum. The mechanical dyssynchrony, although most frequently observed in patients with left bundle branch block, and with QRS duration of 140 ms or greater, it can be observed in patients with a narrow QRS complex. However, resynchronization therapy is not effective in patients with a narrow QRS complexes.

The mechanical dyssynchrony may be associated with decreased stroke volume and cardiac output without a significant change in ventricular volumes. The mechanical dyssynchrony is an important cause of secondary mitral regurgitation in systolic heart failure.

Diastolic Heart Failure

Morphologic changes

In diastolic heart failure, left ventricular cavity size remains normal or can be decreased. Left ventricular end-diastolic volume is normal or less than normal. The end-systolic volume is also decreased, but the magnitude of decrease in end-systolic volume is proportionately greater than that of end-diastolic volume. Thus, left ventricular ejection fraction remains normal. The left ventricular wall thickness is substantially increased in patients with diastolic heart failure. Left ventricular mass is increased in patients with diastolic heart failure. As the cavity size remains normal, the cavity/mass ratio is decreased (**Table 2**).

Reduced cavity size and increased wall thickness are associated with decreased left ventricular wall stress. Decreased wall stress is the predominant mechanism for

Table 2
Systolic versus diastolic heart failure

	SHF	DHF
EDV	Increased	Unchanged or decreased
ESV	Increased	Unchanged or decreased
LVEF	Decreased	Preserved
LV mass	Increased	Increased
LV wall thickness	Unchanged	Increased
LV wall stress	Increased	Decreased

Abbreviations: DHF, diastolic heart failure; EDV, end-diastolic volume; ESV, end-systolic volume; LV, left ventricle; LVEF, left ventricular ejection fraction; SHF, systolic heart failure.

maintaining normal ejection fraction in patients with diastolic heart failure. In patients with a symptomatic diastolic heart, left ventricular volumes remain unchanged and there is no ventricular dilatation. There is, however, increased wall stiffness, which is associated with worsening hemodynamics and symptoms of heart failure.[10,11]

The changes in myocytes in diastolic heart failure are characterized by an increase in its thickness without any change in its length. There is an increase in the thickness of the collagen bundles surrounding the myocytes but the collagen volumes remain unchanged.[6]

Neurohormonal Changes

The neurohormonal changes in systolic and diastolic heart failure are similar.[12] There is an increase in plasma levels of catecholamines. There is also increased activation of the rennin-angiotensin and aldosterone system. Concurrently there is activation of vasodilatory, antimitogenic, and natriuretic peptides. The circulating levels of pro-BNP and BNP are increased in diastolic heart failure.

Although neurohormonal changes in systolic and diastolic heart failure are similar, the effects on ventricular remodeling appear different. In systolic heart failure, there is dilatation of the left ventricle with an increase in end-diastolic and end-systolic volumes. In diastolic heart failure, the ventricular size remains unchanged without an increase in end-diastolic and end-systolic volumes.

Functional Derangements

The principal functional abnormality in diastolic heart failure is increased left ventricular wall stiffness and decreased compliance. The pressure volume relation is shifted upward and to the left. For any given increase in left ventricular volume, there is a disproportionate increase in left ventricular diastolic pressure. The left ventricular contractile function and ejection fraction remain normal; however, some echocardiographic parameters of contractile function may be decreased.

Hemodynamic Changes

Decreased left ventricular compliance is associated with increased left ventricular diastolic pressure. Concurrently, left atrial and pulmonary venous pressures increase with symptoms and signs of pulmonary venous congestion. When there is a marked decrease in left ventricular compliance, left ventricular filling is restricted. As a result, stroke volume and cardiac output decrease with signs and symptoms of low cardiac output. Pulmonary venous hypertension is associated

with an obligatory increase in pulmonary artery pressure. Pulmonary artery pressure is right ventricular afterload and increased pulmonary artery pressure (increased afterload) is associated with right ventricular failure associated with increased right ventricular diastolic and right atrial pressures. Thus, signs and symptoms of systemic venous hypertension, such as peripheral edema, occur despite normal left ventricular ejection fraction.

Diagnosis of Systolic and Diastolic Heart Failure

The symptoms and signs are similar in both systolic and diastolic heart failure. Exertional dyspnea, paroxysmal nocturnal dyspnea, and orthopnea are observed in both types of heart failure. Typical angina is uncommon in patients with systolic or diastolic heart failure. Signs of pulmonary venous congestion, such as pulmonary rales, and of systemic venous congestion, such as elevated jugular venous pressure and lower extremity edema, can be present in both systolic and diastolic heart failure.

Chest radiograph may reveal cardiomegaly and radiologic findings of hemodynamic pulmonary edema (**Fig. 5**). For establishing the diagnosis, however, a transthoracic echocardiography is essential. In patients with systolic heart failure, left ventricular ejection fraction is reduced to less than 45% and in diastolic heart failure, it is normally usually 50% or higher.

Therapeutic Strategies

There are substantial differences in the management of systolic and diastolic heart failure. The neurohormonal antagonists, which have been documented to decrease mortality and morbidity of patients with systolic heart failure, do not appear to be of benefit in patients with diastolic heart failure. Angiotensin inhibitors and adrenergic antagonists, which have been demonstrated as life-saving treatments in systolic heart failure, do not have any beneficial effects in diastolic heart failure. Aldosterone antagonists are useful in the management of patients with advanced systolic heart failure. It remains unclear whether such therapy will be of any benefit in patients with diastolic

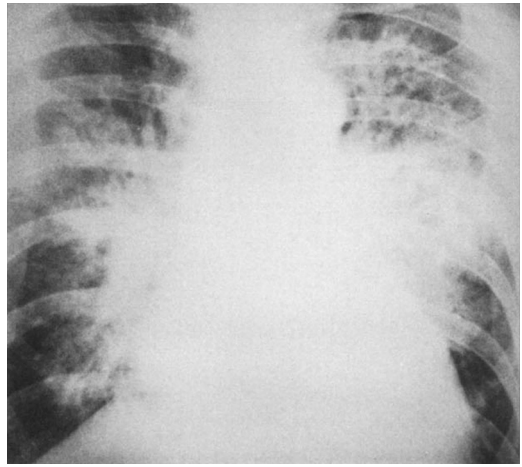

Fig. 5. A plain chest radiograph showing florid hemodynamic pulmonary edema. Pulmonary edema can occur in both systolic and diastolic heart failure.

heart failure. The combination therapy of hydralazine and isosorbide dinitrate produce substantial benefits in reducing mortality and morbidity of patients with systolic heart failure. Such treatment, however, is not effective in patients with diastolic heart failure. Exogenous BNP therapy is not effective in systolic or diastolic heart failure. Nonpharmacologic therapy, such as chronic resynchronization treatment, improves morbidity and mortality of patients with systolic heart failure. Such therapy, however, is not effective in diastolic heart failure. Phosphodiesterase-5 inhibitors may be effective in patients with diastolic heart failure, but they are not effective in patients with systolic heart failure. Forty-four patients with diastolic heat failure with ejection fraction higher than or equal to 50% and pulmonary artery systolic pressure higher than 40 mm Hg were randomized to receive either sildenafil 50 mg 3 times daily or placebo. At 6 and 12 months with sildenafil treatment, there was a significant reduction in mean pulmonary artery, right atrial, and mean pulmonary capillary wedge pressures. There was also a substantial reduction in pulmonary vascular resistance, but systemic vascular resistance and arterial pressure remained unchanged.[13] Thus, the beneficial effect of phosphodiesterase-5 inhibition was attributable to selective pulmonary vasodilatation in these patients. There was a concomitant symptomatic improvement and increased effort tolerance.

Diuretic therapies, however, are necessary to relieve congestive symptoms in both patients with systolic and diastolic heart failure. It should be appreciated that diuretic therapy may worsen the prognosis and cause deterioration of renal function. The treatment strategies in patients with systolic and diastolic heart failure are summarized in **Box 1**.

Box 1
Diastolic and systolic heart failure management strategies

Angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers:

- Decrease mortality and morbidity in systolic heart failure
- Decrease primarily morbidity in diastolic heart failure

Beta-blocker therapy:

- Decrease mortality and morbidity in systolic heart failure
- Unproven benefit in diastolic heart failure

Hydralazine-nitrate:

- Decrease mortality and morbidity in systolic heart failure
- Unproven benefit in diastolic heart failure

PDE-inhibition, beneficial in diastolic heart failure, is contraindicated in systolic heart failure.

Cardiac resynchronization and/or implantable cardioverter defibrillator:

Decrease mortality and morbidity in refractory systolic heart failure

Not indicated in diastolic heart failure

Implantable left ventricular assist device:

May improve short-term survival in selected patients with refractory systolic heart failure

Unproven benefit in diastolic heart failure

Cardiac transplantation:

May be of benefit in both systolic and diastolic heart failure

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